REMARKS

Claims 1, 3 – 5 and 7 – 20, as amended, are pending in the application. Claims 2 and 6 were previously canceled without prejudice. The amendments to claims 1 and 14 were made to provide an explicit transitional phrase (i.e. "comprising") in the claims. The amendments to claims 10, 12, 16, and 19 specify that the dosage formulations are oral dosage formulations. Therefore, no new matter is added.

Reconsideration and re-examination of this application in view of the following remarks is hereby respectfully requested.

I. REJECTION UNDER 35 U.S.C. §103(a)

The previous rejection of claims 1, 3-5 and 7-13 under 35 USC 103(a) as being unpatentable over Anttila (1997) in view of Blom et al. (US 6,984,665) as evidenced by Kangas (1990) is withdrawn based on Applicant's arguments. Claims 1, 3-5 and 7-13 stand rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Anttila in view of DeGregorio et al. (US 5,750,576) and Huebner et al. (US 6,387,920) as evidence by Kangas (1990). This new rejection is respectfully traversed.

The claimed invention as amended is directed to a method for enhancing the bioavailability of orally administered ospemifene or a pharmaceutically acceptable salt thereof (hereinafter "ospemifene" unless otherwise noted). The method comprises administering ospemifene orally to an individual in connection with the intake of a foodstuff having nutritional value and causing secretion of bile acids, being taken shortly before, during or shortly after administering the compound to enhance bioavailability of the compound. Dependent claims further specify preferred dosage ranges and preferred therapeutic uses of ospemifene. The present application discloses that the effect of food intake on ospemifene absorption is 2-3 fold higher than in the fasted state (page 4, lines 4-5). The effect of food also increases the bioavailability of ospemifene in the fed state as compared to the fasted state. (see e.g., Figures 1 and 2).

Anttila teaches that toremifene is an antiestrogen with documented efficacy as an anticancer agent. Anttila conducted a study to determine the effect of food on the bioavailability of toremifene administered orally to healthy volunteers. After evaluating the

results of the study, Anttila concludes that *food does not appear to have an effect on the bioavailability of toremifene citrate* teaching that the drug "can be taken equally well in fasted conditions or with meals." Therefore, Anttila does not teach or suggest that the bioavailability of toremifene is enhanced by co-administering food having nutritional value and causing secretion of bile acids. Moreover, one of ordinary skill in the art would not be able to predict, based on the teachings of Anttila, whether the bioavailability of ospemifene would be impacted by co-administration with food. Therefore, Anttila is deficient in teaching or suggesting the claimed invention.

The DeGregorio et al. reference relates to the use of ospemifene to treat or prevent osteoporosis. The Examiner admits that the DeGregorio reference does not teach the administration of a drug with a meal nor does it teach the use of ospemifene to treat either vaginal atrophy or symptoms thereof. The Examiner alleges that DeGregorio et al. teaches the use of ospemifene in the "treatment of estrogen replacement in postmenopausal women" citing column 1, lines 15-19 of the reference. However, a closer examination of that passage which is in the Background section reveals that DeGregorio is simply stating that the current therapy at that time for postmenopausal osteoporosis was estrogen replacement therapy. DeGregorio et al. does not teach that ospemifene can be used as a replacement for estrogen for any postmenopausal symptom – just osteoporosis as it is defined therein. Therefore, DeGregorio is deficient in teaching or suggesting the claimed invention and its combination with Anttila is likewise deficient.

Huebner et al. relate to structurally unrelated isoxazole estrogen receptor agonist and antagonist compounds. Said compounds are said to have utility in preventing or treating estrogen receptor-mediated disorders such as osteoporosis, breast and endometrial cancers, and the like. Huebner et al. indicate that the isoxazole compounds can be combined with other SERMs, including toremifene, for the treatment of estrogen receptor-mediated disorders. However, Huebner et al. indicate that the compounds have "estrogen receptor-modulating action" (column 87, lines 42-44) a neutral term that indicates that any given compound may be either an estrogen agonist or antagonist in a given tissue. The biological results provided by Huebner et al. confirm that some of the isoxazoles are estrogen agonists and some are estrogen

antagonists in various assays and animal models described therein. Huebner et al. thus illustrate the unpredictability of SERMs in general as compounds that are strict antiestrogens would not be effective in treating osteoporosis and vaginal atrophy (and may actually worsen the conditions) but may have potential to treat breast cancer. Similarly, compounds that are strictly estrogen agonists may have potential in treating osteoporosis and vaginal atrophy but would not be effective in treating breast cancer. Therefore, Huebner et al. cannot be used for the proposition that all of the isoxazoles or other SERMs disclosed therein could be used to treat vaginal atrophy. One must test each compound to determine whether it has a positive or negative impact on the vagina.

In addition, like Anttila and DeGregorio et al., Huebner et al. is silent regarding orally administering any compound, much less ospemifene, to an individual in connection with the intake of a foodstuff having nutritional value and causing secretion of bile acids, being taken shortly before, during or shortly after administering the compound to enhance bioavailability of the compound. Therefore, Huebner et al. is deficient in teaching or suggesting the claimed invention and its combination with Anttila and/or DeGregorio is likewise deficient.

Kangas establishes that ospemifene is a minor metabolite of toremifene. Kangas is silent regarding orally administering any compound, much less ospemifene, to an individual in connection with the intake of a foodstuff having nutritional value and causing secretion of bile acids, being taken shortly before, during or shortly after administering the compound to enhance bioavailability of the compound. Therefore, Kangas is deficient in teaching or suggesting the claimed invention and its combination with Anttila and/or DeGregorio and/or Huebner et al. is likewise deficient.

Applicant respectfully points out that the Examiner makes several factual and/or technical errors that appear to negatively influence the patentability analysis. Applicant singles out these errors because they form important bases in the Examiner's rejection and the Examiner did not address applicant's argument in the current office action. Applicants provide herewith the Declaration of Risto Lammintausta, M.D., Ph.D. and respectfully asks the Examiner to consider the following points, further covered in the Declaration:

Error No. 1: Anttila discloses administering 60 mg/day of a metabolite of toremifene.

Not true. Anttila discloses administering 60 mg tablets of toremifene. There is no mention of administering metabolites of toremifene. Blood levels of a major metabolite of toremifene, namely N-demethyltoremifene (or desmethyltoremifene), were measured, but no metabolite was administered.

Error No. 2: Administration of a drug that metabolizes to the active form *in vivo* is the same as administering the metabolite.

This is only true in the case of prodrugs. This is not the case with, for example, toremifene, where the parent drug is the most active compound and thus dominates the clinical tissue specific profile of toremifene. In this case, ospemifene is a minor metabolite of toremifene which does not contribute to the effect of toremifene and its main metabolite desmethyltoremifene as breast cancer treatment compounds. Ospemifene in therapeutic doses demonstrates a therapeutic profile to treat vaginal atrophy, an estrogen agonizing effect, which is an opposite effect versus that of toremifene antagonizing the estrogen effect. Although ospemifene and toremifene are structural relatives, their pharmacokinetics are significantly different: when ospemifene has elimination half-life of one week, ospemifene is metabolized much faster, with elimination half-life of one day. The metabolites of ospemifene, 4-OH and 4'-OH ospemifene are active compounds contributing to the effect of ospemifene in vaginal atrophy, but these metabolites are not formed from toremifene at all.

Error No. 3: Food…would inherently enhance bioavailability of toremifene.

Not true. The Examiner provides no basis for this conclusion. The Anttila reference teaches that toremifene "works equally well with or without administration of food." This is not evidence of inherency but is rather evidence of a teaching away. Furthermore, inherency is only relevant in an anticipation context and has very limited applicability in an obviousness context. Given the findings in Anttila and unpredictability of SERMs in general, the skilled artisan could not have predicted that co-administering ospemifene with food in an amount that causes secretion of bile acids would enhance the bioavailability of ospemifene.

Error No. 4: [It] would have been obvious to...substitute one SERM drug for another.

Not true. The scientific literature clearly establishes that SERMs may be either estrogen agonists or antagonists in a given tissue and most exhibit varying degrees of estrogenic and antiestrogenic actions. For example, toremifene is an approved therapy for breast cancer (e.g. acts as an estrogen antagonist in breast tissue) while raloxifene is indicated for the treatment and prevention of osteoporosis (e.g. an estrogen agonist in bone) and is now indicated for the reduction in risk of breast cancer (e.g. an estrogen antagonist in the breast). Some SERMs act as estrogen agonists in the uterus which would tend to increase the likelihood of endometrial cancer. In other words, it is not obvious that one could substitute a novel SERM for another SERM as its exact effects on a series of tissue is not known until tested. Therefore, one would not be motivated to substitute one particular SERM for another in any given therapeutic application absent additional teachings.

A finding of obviousness requires that the prior art both suggest the invention and provide one of ordinary skill with a reasonable expectation of success. *In re O'Farrell* 853 F.2d 894, 903, 7 USPQ2d 1673 (Fed. Cir. 1988). Secondary considerations such as unexpected results must be considered if present. *Stratoflex, Inc. v. Aeroquip Corp.,* 713 F.2d 1530, 1538-39, 218 USPQ 871, 879 (Fed. Cir. 1983); *In re Merck & Co., Inc.,* 800 F.2d 1091, 1096, 231 USPQ 375, 378 (Fed. Cir. 1986). The USPTO must consider rebuttal evidence of teaching away. *See In re Sullivan*, 84 USPQ2d 1034, 1038 (Fed. Cir. 2007) (The Federal Circuit remanded an appeal back to the BPAI for failure to consider rebuttal evidence put forth by the Applicant during prosecution).

Applicants submit that the cited prior art does not provide one of ordinary skill in the art with a reasonable expectation of success. Additionally, the evidence set for in Anttila, the primary reference used in rejection teaches away from a food effect for ospemifene. Further, it was unexpected that the effect of food intake on ospemifene absorption would be 2-3 fold higher than in the fasted state and that the effect of food would increase the bioavailability of ospemifene in the fed state as compared to the fasted state. Therefore, in light of the amendments and arguments above, applicant respectfully requests reconsideration and withdrawal of the obviousness rejection.

II. FIRST REJECTION FOR OBVIOUSNESS-TYPE DOUBLE PATENTING

Claims 1, 3-5 and 7-20 stand rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 5-6, 10 and 13-28 of U.S. Patent Application No. 11/201,098 (US 2005/0272825). The Examiner argues that whether or not the instant claims are directed to bioavailability there is no distinguishing step that indicates once the drug is administered it would not treat urinary symptoms. Applicant respectfully disagrees. As pointed out in a prior office action, the Examiner has already taken the position that "food can be an active agent as it comprises nutrients for the functioning of the body." Office Action dated April 30, 2008, page 6. Applicant points out that one distinguishing step between the claimed invention and the prior art is the administration of ospemifene after prompting a bile-rich environment in the gastrointestinal tract.

The Examiner argues that because Vasu teaches that drugs are known to be commonly administered with food or without food that this would motivate one to combine the prior art references to achieve the claimed invention. Applicant points out that in order for there to be motivation to combine references in a way to suggest a claimed invention, one of ordinary skill in the art must have a reasonable expectation of success. One of ordinary skill in the art had no expectation that administering ospemifene slightly before, during or after food intake would have such a dramatic positive effect on the oral bioavailability of the drug. Rather, the prior art actually taught away from the invention as we have specifically set forth in prior replies. Further, applicant reminds the Examiner that "[p]atentability shall not be negatived by the manner in which the invention was made." 35 U.S.C. 103(a), last sentence.

Applicant respectfully submits that claims 1, 3-5 and 7-20 should not be rejected for obviousness-type double patenting over the '098 patent application, in view of the teaching away of Anttila, and the unexpected results in disclosed in the specification. Therefore, Applicant respectfully requests that the obviousness-type double patenting rejection of claims 1, 3-5 and 7-20 over US Application No. 11/201,098 be withdrawn.

III. SECOND REJECTION FOR OBVIOUSNESS-TYPE DOUBLE PATENTING

Claims 1, 3-5 and 7-20 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 of U.S. Patent No. 6,984,665 ("the '665 patent"). The Examiner argues that as evident by Vasu, drugs are known to be administered with food. In reply, applicant agrees that it is known that drugs are administered with food, but one would not have known the effect of co-administering food under the claimed conditions. Food can have positive, negative, or neutral effects on the bioavailability of drugs and the nature and extent of those effects cannot typically be known until empirically tested as applicants have done here. For the reasons set forth above in response to the first rejection of the claims for obviousness-type double patenting, applicant similarly maintains that claims 1, 3-5 and 7-20 should not be rejected for obviousness-type double patenting, in view of the teaching away of Anttila, and the unexpected results in disclosed in the specification. Therefore, Applicant respectfully requests that the obviousness-type double patenting rejection of claims 1, 3-5 and 7-20 over the '665 patent be withdrawn.

IV. THIRD REJECTION FOR OBVIOUSNESS-TYPE DOUBLE PATENTING

Claims 1, 3-5 and 7-20 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 of U.S. Patent No. 6,245,819 ("the '819 patent").

The Examiner cites the '819 patent in rejection but cites portions of the '665 patent in rejection. While there are many passages of the '819 patent that are contained in the '665 patent, the Examiner cites portions of the '665 patent that are not contained in the '819 patent. As argued above, the '665 patent is deficient in teaching or suggesting the claimed invention. In the same way, the '819 patent is deficient as it is silent regarding improving bioavailability of ospemifene by co-administration of food. For the reasons set forth above in response to the first rejection of the claims for obviousness-type double patenting, applicant similarly maintains that claims 1, 3-5 and 7-20 should not be rejected for obviousness-type double patenting, in view of the teaching away of Anttila, and the unexpected results in disclosed in the specification. Therefore, Applicant respectfully requests that the obviousness-type double patenting rejection of claims 1, 3-5 and 7-20 over the '819 patent be withdrawn.

In view of the above amendments and remarks, it is submitted that the claims are in condition for immediate allowance. The Examiner is invited to contact the undersigned attorneys for the Applicant via telephone if such communication would expedite this application.

Respectfully submitted,

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